Treating Patients with Metastatic Castration Resistant Prostate Cancer: A Comprehensive Review of Available Therapies

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Purpose: The availability of newly approved treatment options for metastatic castration resistant prostate cancer is not matched with conclusive data on optimal sequencing strategies and resistance patterns. A comprehensive review of efficacy and safety data for new agents and current knowledge regarding treatment sequencing would enable treating physicians to make rational drug selections in patients with metastatic castration resistant prostate cancer.

Materials and Methods: We searched MEDLINE® and relevant congresses for data on cabazitaxel, docetaxel, ^{223}radium dichloride, abiraterone, enzalutamide and sipuleucel-T, focusing on sequencing strategies, resistance mechanisms and biomarkers of response.

Results: Abiraterone and enzalutamide target the androgen axis with different mechanisms of action. Abiraterone blocks cytochrome P450 17, inhibiting androgen synthesis, whereas enzalutamide inhibits androgen receptor, reducing nuclear translocation of the androgen receptor complex and subsequent DNA binding. Both agents provide improved overall survival in patients with metastatic castration resistant prostate cancer who received prior docetaxel treatment and in those who are chemotherapy naïve. Cabazitaxel provides improved overall survival in patients with metastatic castration resistant prostate cancer with prior docetaxel therapy. Sipuleucel-T provides improved overall survival in asymptomatic patients and ^{223}radium provides improved overall survival in chemotherapy naïve and chemotherapy treated patients with symptomatic bone metastases. Selecting the correct treatment with metastatic castration resistant prostate cancer is complex as no head-to-head trials have been done and comparison between existing trials is difficult due to differences in

Abbreviations and Acronyms

ADT = androgen deprivation therapy

AE = adverse event

AR = androgen receptor

AR-V = AR splice variant

COU-AA-302 = Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients with mCRPC

CTC = circulating tumor cell

CYP17 = cytochrome P450 17

FDA = Food and Drug Administration

mCRPC = metastatic castration resistant prostate cancer

OS = overall survival

PFS = progression-free survival

PREVAIL = Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients with Progressive Metastatic Prostate Cancer

PSA = prostate-specific antigen

QoL = quality of life

rPFS = radiographic progression-free survival

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study populations and a lack of validated biomarkers. Factors to consider include prior therapy, symptom burden, metastasis type, performance status, comorbidities, adverse event profiles and patient preference. Another consideration is treatment sequence since some agents affect responses to subsequent choices. For example, resistance to abiraterone or enzalutamide may result in limited responses to subsequent androgen targeted agents. Identifying factors predictive of resistance is an area of ongoing research with androgen receptor variants representing a good candidate. Prognostic factors for survival are also likely to be useful and are currently being studied.

Conclusions: New therapies for metastatic castration resistant prostate cancer have brought new challenges with regard to treatment selection and sequencing. While hormonal agents provide good therapeutic responses, resistance may be intrinsic without prior drug exposure. Identifying predictors of response and relevant biomarkers will allow therapies to be more precisely tailored to individual patient profiles.

Key Words: prostatic neoplasms, neoplasm metastasis, castration, drug therapy, androgen antagonists

For many years the mainstay of treatment for mCRPC was docetaxel. Since 2010, several treatments have shown a survival benefit in patients with mCRPC in phase 3 trials, leading to regulatory approval and subsequent inclusion in treatment guidelines (table 1).[1]

Despite the numerous treatment options for mCRPC the impact on survival is less than optimal and there are limited data to provide guidance regarding how to optimally sequence approved treatments for individual patients. Recently results from several studies of mCRPC began to identify clinical factors that predict benefit from androgen axis targeted and other therapies, which might help inform treatment decisions for individual patients. This article provides an overview of phase 3 trial data for androgen axis targeting agents in mCRPC as well as perspectives on other recently approved mCRPC agents, a review of studies attempting to assess the impact of resistance to androgen axis targeting agents and emerging data on prognostic factors and biomarkers in patients with mCRPC.

METASTATIC CASTRATION RESISTANT PROSTATE CANCER TREATMENT EVOLUTION

The benefits of recently approved treatments for mCRPC have been shown in 7 randomized phase 3 trials (table 2).

Trials of Androgen Axis Targeting Agents

After Chemotherapy. Abiraterone and enzalutamide target the androgen axis. Abiraterone inhibits androgen synthesis by the adrenal glands and testes, and within the prostate tumor by blocking CYP17, a critical enzyme in testosterone synthesis.[2] In contrast, enzalutamide targets AR, including intracellular signaling functions.[3]

The efficacy of abiraterone and enzalutamide in mCRPC was proved initially in men who had received prior docetaxel chemotherapy. In the abiraterone trial 1,195 patients received prednisone 5 mg twice daily in combination with oral abiraterone 1,000 mg once daily or placebo.[2,4] In the enzalutamide trial 1,199 patients received oral enzalutamide 160 mg daily or placebo.[3] After 20.2 months of median followup in the abiraterone trial OS was longer for abiraterone/prednisone vs placebo/prednisone (median 15.8 vs 11.2 months, $p < 0.001$).[4] In the enzalutamide trial, which was reported with shorter followup (median 14.4 months), OS was also longer for enzalutamide vs placebo (median 18.4 vs 13.6 months, $p < 0.001$).[3] For both agents superiority vs the control arm was demonstrated for other end points, including standard assessments (PSA response rate, tumor response, time to PSA progression and rPFS) as well as other end points (time to skeletal events, pain palliation and health related QoL).[2–6]

AEs that were more frequent for abiraterone/prednisone vs placebo/prednisone included urinary tract infection in 12% vs 7% of patients ($p = 0.02$), fluid retention/edema in 31% vs 22% ($p = 0.04$) and hypokalemia in 17% vs 8% ($p < 0.001$) with the latter 2 AEs attributable to mineralocorticoid excess resulting from CYP17 blockade.[2] AEs that appeared more frequent for enzalutamide vs placebo treatment included fatigue in 34% vs 29% of cases, diarrhea in 21% vs 18%, hot flashes in 20% vs 10%, musculoskeletal pain in 14% vs 10%, headache in 12% vs 6%, hypertension in 7% vs 3% and seizures in 0.6% vs 0%.[3]

Overall each trial provided confirmation that mCRPC remains in part an androgen driven disease